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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,496	01/31/2002	Eldon Emberly	15157	5187

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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,496	EMBERLY ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments filed August 13, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Claims 1-28 are examined on the merits.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. NEW MATTER REJECTION.

5. The instant rejection has been necessitated by Applicant's claim amendment.

6. Claim 13, lines 2-3, recites the new limitation of "applying a predetermined constraint value" which has not been found in instant specification as originally disclosed. It is noted that claim 13 as originally filed recites the generic limitation of "predetermined constraint" which is different from the new limitation of "applying a predetermined constraint value." Further, the instant specification discloses " user-supplied constraint...to mean a

predetermined criterion for reducing the number of stacks in a set" ([0039]) which is also different from the new limitation of "applying a predetermined constraint value." Claim 14 is rejected for being dependent from claim 13.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. This rejection is maintained with respect to claims 26-28, as recited in the previous office action mailed March 11, 2004.

10. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic

engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

RESPONSE TO ARGUMENTS

11. Applicant argues that any "choice of h_o lead to a particular set of 100 most designable 4-helix....The value of h_o is adjusted so that the top 100 stacks have approximately the same compactness as natural 4-helix bundles...This best fit is shown in Figure 5 of the instant specification." Applicant's argument has been fully considered and found to be unpersuasive. It is noted that page 8 of the instant specification discloses "Figure 5 is a best fit of surface distribution of the 11 SCOP proteins to top 100 designable structures found using h_o = 2kbT." The pointed to disclosure does not support Applicant's assertion that the "choice of h_o lead to a particular set of 100 most designable 4-helix" because the top 100 designable structures depends on h_o via the equation h_o = 2kbT wherein the parameters within said equation have not been clearly defined. The instant specification does not provide guidance as to how one of skill in the art would determine by fitting the surface-area distribution of a set of natural four-helix bundles to the surface-area distributions for the 100 most designable four-helix-stacks. What fitting criteria are being used to select the 100 most designable four-helix-stacks to calculate h_o? How does one of skill in the art arrive at the values of h_o = 2kbT and hydrophobic residues have a hydrophobicity of 5kbT and polar residues –1kbT?

REJECTION RE-ITERATED

12. Specific to the equation for determining $E_{designability}$ of claim 26, the term h_i has not being defined in the specification to the extend which would enable one of skill in the art to

predictably practice the claim invention as recited by claims 26-28 without any undue experimentation. It is noted the instant specification discloses that $h_i = h_o$ +/- δh and h_o is determined by fitting the surface-area distribution of a set of natural four-helix bundles to the surface-area distributions for the 100 most designable four-helix-stacks. The best fit preferably corresponds to $h_o = 2kbT$ and hydrophobic residues have a hydrophobicity of $5k_bT$ and polar residues $-1k_bT$. However, the instant specification does not provide guidance as how one of skill in the art would determine by fitting the surface-area distribution of a set of natural four-helix bundles to the surface-area distributions for the 100 most designable four-helix-stacks. What fitting criteria are being used to select the 100 most designable four-helix-stacks to calculate h_o? How does one of skill in the art arrive at the values of $h_o = 2kbT$ and hydrophobic residues have a hydrophobicity of $5k_bT$ and polar residues $-1k_bT$? Therefore, one of skill in the art would not be able to predictably practice the claimed invention as directed to determining $E_{designability}$ without knowing how h_i is derived via h_o.

CLAIM REJECTIONS - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-8, 13-15, 20, 23, and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Dahiyat et al. (1997).

15. This rejection is maintained with respect to claims 1-8, 13-15, 20, 23, and 24, as recited in the previous office action mailed March 11, 2004.

RESPONSE TO ARGUMENTS

16. Applicant argues that the disclosure of Dahiyat et al. can only be practiced from a starting point of a predetermined backbone configuration, while the claimed invention provides a method for designing new stable backbone configurations. Applicant's argument has been fully considered and found to be unpersuasive because the instant claims do not recite the argued limitation of "designing new stable backbone configurations." Therefore, the citation of said limitation is not required from the instant prior art for anticipation basis.

17. It is noted that the claims are given their broadest reasonable interpretation consistent with the specification. However, the instant claims are not limited to the limitations that have been cited from the specification by Applicant as limitations that are not disclosed by the cited prior art. As cited by the MPEP, the court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (MPEP §2111 [R-1]).

REJECTION RE-ITERATED

18. Dahiyat et al. discloses a method for designing stable and well-folded (backbone configurations) proteins with novel sequences wherein said method comprises specifying a protein having less than 30 residues containing sheet, helix, and turns structures (page 82, Abstract etc. and column 3, lines 32-34). The method of Dahiyat et al. is directed toward the

screening of possible sequences for compatibility with the desired protein fold (designable) (page 82, column 1, lines 12-16) and select an amino acid sequence that will stabilize a target structure (designable) (page 82, column 2, lines 4-7), as in instant claim 1, step a, and claims 2-4.

19. The arrangement of these secondary structural elements is directed to the core and boundary position of the protein in regard to side chains, protein coil-coil designs, and hairpin turns (stack as defined by the instant specification) (page 83, column 1 to column 2, line 19; and Figure 4), as in instant claim 1, steps b and c.

20. An alignment of the sequences indicates only 6 of the 28 residues are identical and four of the identities are in the buried cluster (page 83, column 3, lines 7-14), as in instant claims 5-7.

21. The method of Dahiyat et al. comprises sedimentation equilibrium studies directed at randomly distributed residuals (page 87, References and Notes, No. 27 and 28), restrained energy minimized average from the NMR structure determination as directed to Ω and X1 and X2 angles (Euler angle), and Cα coordinates (page 86, Table 2), as in instant claim 8.

22. The packing pattern of the hydrophobic core of the NMR structure is used to determine the constraint criteria as directed to matching X1 and X2 angles, the agreement of the strand-to-helix turn, and the difference in the Φ and Ψ angles for sequence selection (page 86, column line 1 to column 2, line 34), as in instant claims 13 and 14.

23. The NMR data were collected NMR spectrometry wherein water suppression was accomplished either with pre-saturation during relaxation delay or pulsed filed gradients (page 87, References and Notes, No. 28), as in instant claim 15.

24. The total number of amino acid sequences that must be considered is the product of the number of possible amino acid at each residue position (page 83, column 1, lines 23-28) and the respective residues are classified by ranking (cluster) (Figure 1), as in instant claim 20.

25. The design algorithm of Dahiyat et al. designs proteins based on the following criteria distance restraint (constraint), protein-folding characteristics of a motif with a small hydrophobic ore, and the protein backbone is defined with a root-mean-square (rms) (page 85, columns 1-3, Experimental Validation §). Based on the criteria above, the design algorithm of Dahiyat et al. select for optimal sequence from nonoptimal sequences (Figure 1), as in instant claims 23 and 24.

CLAIM REJECTIONS - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (1997) taken with Dahiyat et al. (US006403312B1).

29. This rejection is maintained with respect to claims 1-25, as recited in the previous office action mailed March 11, 2004.

RESPONSE TO ARGUMENTS

30. Applicant's argument directed to the primary reference, Dahiyat et al. (1997), has been fully considered and found to be unpersuasive as discussed in the above 35 USC §102(b) rejection.

RESPONSE TO ARGUMENTS

31. Dahiyat et al. (1997) discloses the limitations to claims 1-8, 13-15, 20, 23 and 24 as discussed above.

32. However, Dahiyat et al. (1997) does not disclose the step of generating an initial stack by the conjugate gradient method as in claim 9.

33. Dahiyat et al. (US006403312B1) discloses a method for protein design comprising a step of using the conjugate gradient method for the computational prescreening process (column 30, Example 1), as in instant claim 9.

34. The above disclosure of Dahiyat et al. (1997) has been extended to claims 10, 16-18, 21, and 22. Further, the comparison of the FSD-1 and the design target is analyzed in stereoview using the best-fit superposition (symmetry) of the restrained energy minimized average NMR structure (Figure 6), as in instant claims 11 and 12.

35. "This hydrogen bond is present in 95 percent of the structure ensemble and has a donor-acceptor distance of 2.6 +/- 0.06 A" (about 1.5 Angstroms) (Dahiyat et al. (1997), page 86, column 1, lines 34-44), as in instant claim 19.

36. The design algorithm of Dahiyat et al. (1997) provides a means for calculating surface exposure values (Dahiyat et al. (1997), page 87, References and Notes, No. 15), as in instant claim 25.

37.

38. Dahiyat et al. (1997) discloses an improvement for designing stable, well-folded proteins with a fully automated novel sequence selection (Abstract etc. and page 82, column 1, lines 1-3).

39. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement disclosed by Dahiyat et al. (1997) to design stable, well-folded proteins with a fully automated novel sequence selection using a protein library as taught by Dahiyat et al. (US006403312B1). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to design stable, well-folded proteins with a fully automated novel sequence selection using a protein library as taught by Dahiyat et al. (1997) and Dahiyat et al. (US006403312B1).

CONCLUSION

40. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

41. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

42. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

43. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

44. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

45. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

46. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

C. Dune Ly

10/21/04

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
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